

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

07 JUL 2004

To:

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B-41 Nizamuddin East
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PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY EXAMINATION
REPORT

(PCT Rule 71.1)

Date of mailing

29 JUN 2004

Applicant's or agent's file reference
113521PCT59

IMPORTANT NOTIFICATION

International Application No.

PCT/IN2003/000383

International Filing Date

5 December 2002

Priority Date

5 December 2001

Applicant

BLU CON INDIA LIMITED and

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with form PCT/IB-501).

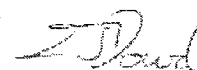
Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/AT

AUSTRALIAN PATENT OFFICE
PO BOX 200 WOODHILL ACT 2606 AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
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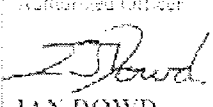
Authorized Officer


IAN DOWD

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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 34, 35 and 36)

Applicant's or agent's file reference 11/526(PCT/59)	FOR FURTHER ACTION	Name of the International Preliminary Examining Authority International Preliminary Examining Report (Form PCT/ISPE/4)
International Application No. PCT/IN2003/000383	International Filing Date <i>(date in which it is)</i> 5 December 2003	Priority Date (date in which report) " (date in which report)
International Patent Classification (IPC) or national classification and IPR Int. Cl. C 07D 492/18		
Applicant BIOCON INDIA LIMITED et al		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 2 sheets, including the cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings, which have been amended and are the basis for this report and of sheets containing recitations made before this Authority (see Rule 50.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 3 sheets.		
3. This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application		
Date of submission of the demand 22 March 2004	Date of completion of the report 24 June 2004	
Name and mailing address of the IPEA A: AUSTRALIAN PATENT OFFICE PO BOX 200, WOMEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6283 3929	Authorized Officer  IAN DOWD Telephone No. (02) 6283 3273	

I. Basis of the report

1. With regard to the elements of the international application:

☐ the international application as originally filed☒ the description, pages 2-7, as originally filed

pages 1, filed with the demand

pages 1, received on 18 June 2004, with the letter of 16 June 2004

☒ the claims, pages 9-10, as originally filed

pages 1, as amended (submitted with the demand under Article 19)

pages 1, filed with the demand

pages 8, received on 18 June 2004, with the letter of 16 June 2004

☐ the drawings, pages 1, as originally filed

pages 1, filed with the demand

pages 1, received on 18 June 2004, with the letter of 16 June 2004

☐ the sequence listing part of the description

pages 1, as originally filed

pages 1, filed with the demand

pages 1, received on 18 June 2004, with the letter of 16 June 2004

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

☐ these elements were available or furnished to this Authority in the following language, which is:☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)),☐ the language of publication of the international application (under Rule 48.1(b)),☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 75.2 and/or 75.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form☐ filed together with the international application in computer readable form☐ furnished subsequently to this Authority in written form☐ furnished subsequently to this Authority in computer readable form☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished4. ☐ The amendments have resulted in the cancellation of:☐ the description, pages☐ the claims, Nos.☐ the drawings, sheets fig.5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been forwarded to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.1(f) and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (IX)	Claims 1-10	YES
	Claims	NO
Inventive step (IX)	Claims 1-10	YES
	Claims	NO
Industrial applicability (IX)	Claims 1-10	YES
	Claims	NO

2. Citations and explanations (Rule 79(2))

This report is based on the documents cited in the International Search Report.

- D1 US 5 508 398 A1
- D2 US 5 616 595 A1
- D3 US 4 734 492 A1
- D4 J. Antibiot (Tokyo) 1990 May; 52(5): 366-73
- D5 US 6 576 135 B1
- D6 US 6 492 513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step

Industrial Applicability

All claims satisfy the requirements of industrial applicability

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 34 and Part 7)

Applicant's or agent's file reference 11352(PCT/59)	<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;">FOR FURTHER ACTION</div> <div style="width: 70%;">see Notification or Transmittal or International Preliminary Examination Report (Form PCT/IBEA/76)</div> </div>	
International Application No. PCT/IN2003/000383	International Filing Date <i>(day month year)</i> 5 December 2003	Priority Date <i>(day month year)</i> 5 December 2003
International Patent Classification (IPC) or national classification (e.g. JP) Int. Cl. C 001D 498/18		
Applicant BIOCON INDIA LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 35.


2. This RI-PREL consists of a total of 5 sheets, including the cover sheet.

☒ This report is also accompanied by ANNEXes, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or Annexes containing rectifications made before this Authority (see Rule 70.16 and Section 60 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22 March 2004	Date of completion of the report 24 June 2004
Name and mailing address of the IPEA/AL AUSTRALIAN PATENT OFFICE PO BOX 200, WOOLLEN, ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. 60216285 3929	Authorized Officer  IAN DOWD Telephone No. 60216285 2273

1. Basis of the report

1. With regard to the elements of the international application:

☐ the international application as originally filed☒ the description, pages 2-7, as originally filed,

pages 1, filed with the demand,

pages 1, received on 18 June 2004 with the letter of 16 June 2004

☒ the claims, pages 9-10, as originally filed,

pages 1, as amended together with amendments under Article 10,

pages 1, filed with the demand,

pages 8, received on 18 June 2004 with the letter of 16 June 2004

☐ the drawings, pages 1, as originally filed,

pages 1, filed with the demand,

pages 1, received on 18 June 2004 with the letter of 16 June 2004

☐ the sequence listing part of the description

pages 1, as originally filed,

pages 1, filed with the demand,

pages 1, received on 18 June 2004 with the letter of 16 June 2004

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language, which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b))☐ the language of publication of the international application (under Rule 48.2(b))☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3)

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form☐ filed together with the international application in computer-readable form☐ furnished subsequently to this Authority in written form☐ furnished subsequently to this Authority in computer-readable form☒ The sequence listing as filed in the international application as filed has been furnished☐ The statement that the information recorded in computer-readable form is identical to the written sequence listing has been furnished4. ☐ The amendments have resulted in the cancellation of:☐ the description, pages☐ the claims, Nos.☐ the drawings, sheets/figs5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.12) **

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 4 and annexed to this report.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-10	YES
	Claims	NO
Inventive step (IS)	Claims 1-10	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-10	YES
	Claims	NO

2. Citations and explanations (Rule 59.3)

This report is based on the documents cited in the International Search Report

- D1 US 5 508 398 A1
- D2 US 5 616 595 A1
- D3 US 4 734 497 A1
- D4 J. Antibiot (Tokyo) 1980 May; 52(5): 466-73
- D5 US 6 576 135 B1
- D6 US 6 497 513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step

Industrial Applicability

All claims satisfy the requirements of industrial applicability

5 **TITLE OF THE INVENTION**

PROCESS FOR THE PURIFICATION OF MACROLIDES

FIELD OF THE INVENTION

This invention relates to a process for purification of macrolides.

10 **BACKGROUND OF THE INVENTION**

A compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25, 26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methyl ethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS), also known as FK506 as well as tacrolimus disclosed by EP 184162 and US 4,894,366 is useful as an immunosuppressant. Another compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26, 26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S,4R,5S,8R,9E,12S,14S, 15R,16S,18R,19R,26aS)-, also known as immunomycin as well as FK 520, disclosed in EPO Publication No. 0184162 is also useful as an immunosuppressant. Many other derivatives of these compounds as well as structural analogues have immunosuppressant property.

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5 We claim:

1. A process for the recovery of a macrolide in substantially
pure form comprising:
 - a) treatment of an impure or crude macrolide with water
immiscible solvent,
 - 10 b) optional concentration of the mixture,
 - c) treatment with ammonia gas to phase out impurities,
 - d) separation of impurities,
 - e) optional concentration of the phase containing the
macrolide,
 - 15 f) loading on silica gel chromatography, optionally
reversed phase or pretreated with silver, and elution of
the macrolide,
 - g) affording the macrolide in substantially pure form,
 - h) optional repetition of step f and g to afford the
20 macrolide in substantially pure form.
2. A process as in claim 1, wherein the macrolide is selected
from tacrolimus, immunomycin or sirolimus.
3. A process as in claim 1, wherein the water immiscible solvent
is selected from a group comprising hydrocarbons,
25 heterocyclic compounds, ethers or esters.
4. A process as in claim 1, wherein the water immiscible
solvents is selected from a group comprising benzene,
toluene, hexane, ethyl acetate, isobutyl acetate or butyl
acetate.
- 30 5. A process as in claim 1, wherein the macrolide compound is
afforded by crystallization or precipitation.